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THE INFLUENCE OF CERTAIN OXIDIZING AGENTS (SODIUM IODOSOBENZOATE AND SODIUM IODOXYBENZOATE) ON PHAGOCYTOSIS.*

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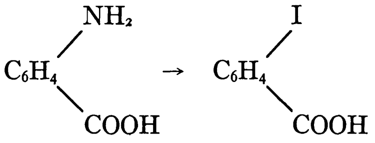
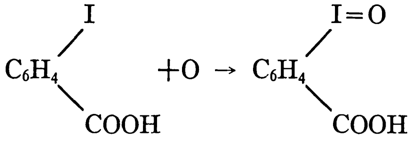
Sodium iodosobenzoate and sodium iodoxybenzoate were first prepared by Victor Meyer[1] and his co-workers. They are made from iodbenzoic acid by oxidation. Iodbenzoic acid is made from anthranilic acid (ortho-amido benzoic acid) by treating it with sodium nitrite and potassium iodid in acid solution:



$$C_6H_4\begin{cases}NH_2\\COOH\end{cases} \rightarrow C_6H_4\begin{cases}I\\COOH\end{cases}$$

Iodosobenzoic acid is prepared by oxidation of ortho-iodbenzoic acid with potassium permanganate in acid solution. This acid has a melting-point of 226°, and crystallizes in large leaves or in needles from dilute solution:



$$C_6H_4\begin{cases}I\\COOH\end{cases} + O \rightarrow C_6H_4\begin{cases}I=O\\COOH\end{cases}$$

Ostwald[2] demonstrated that this substance is one of the weakest of acids, its dissociation constant being less than that for carbonic acid:

K for iodbenzoic acid	0.132
K for iodosobenzoic acid	0.00006
K for carbonic acid	0.0013

The above property is made use of in the purification of iodosobenzoic acid, by precipitation from solution in sodium hydroxid with carbonic acid.

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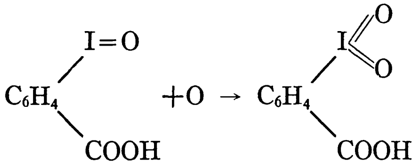
[1] Meyer and Wachter, *Berichte d. d. chem. Ges.*, 1892, 25, p. 2632; Askenasy and Meyer, *ibid.*, 1893, 26, p. 1354; Hartmann and Meyer, *ibid.*, 1893, 26, p. 1727; *ibid.*, 1894, 27, p. 1600.

[2] *Ibid.*, 1893, 26, p. 1359.

Iodoxybenzoic acid is made from iodosobenzoic acid by oxidation with chlorine:



This substance has marked acid properties. It crystallizes in small glistening needles. The preparation of these substances has been discussed by Loevenhart and Grove.[1]

The action of these substances was first studied by Heinz[2] in 1899. Heinz attempted to study the action of nascent iodin in the body by their use. He was, however, dealing with an impure substance, for his preparations were yellow in color.

The pharmacological action of these compounds has been studied by Loevenhart and Grove and by Loevenhart and the author. These investigations demonstrated that sodium iodosobenzoate and sodium iodoxybenzoate oxidize hemoglobin to oxyhemoglobin, and that sodium iodosobenzoate can furnish oxygen for the peroxidase reaction by oxidizing phenolphthalin to phenolphthalein in the presence of blood. The substances cause no destruction of the blood on intravenous injection, but cause a moderate leukocytosis. They cause a fall of blood pressure on intravenous injection chiefly by depression of the vasomotor center.

Sodium iodosobenzoate and iodoxybenzoate, which contain oxygen, cause cessation of respiration, or apnoea, especially in cats. The respiratory center is most sensitive to these substances, next the vasomotor center. This activity must be due to the oxygen combined with the iodin in them, for sodium iodbenzoate has no such effect.

That their action is due to the available oxygen is further demonstrated by the antagonism between hydrocyanic acid and sodium iodosobenzoate in regard to the respiratory center, as demonstrated by Grove and Loevenhart.[3]

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[1] *Jour. Pharm. and Exper. Ther.*, 1911, 3, p. 101.

[2] *Virchow's Arch.*, 1899, 155, p. 44.

[3] *Jour. Pharm. and Exper. Ther.*, 1911, 3, p. 131.

During a study of the effect of these substances on animals in infection I[1] made an investigation of their antiseptic and germicidal action. I found that sodium iodosobenzoate and sodium iodoxybenzoate have a marked germicidal action toward the colon bacillus, the typhoid bacillus, etc., whereas sodium iodbenzoate has very little action. The relative germicidal action toward the colon bacillus was as follows:

Substance	Amount of Oxygen	Concentration Required to Kill	Relative Bactericidal Action
Sodium iodbenzoate.........	None	N/10 (2.7 per cent)	1
Sodium iodosobenzoate........	6.06 per cent	N/1,000 (0.028 per cent)	100
Sodium iodoxybenzoate......	11.43 per cent	N/2,000 (0.015 per cent)	200

These results indicate that sodium iodosobenzoate and sodium iodoxybenzoate have marked germicidal properties, and that this action must be due to the oxygen present in the molecules. Furthermore, the germicidal action is not destroyed by the presence of serum.

The influence of sodium iodoxybenzoate on the production of antibodies in dogs has been studied by Hektoen.[2] Dogs receiving this substance intravenously produced more antibodies than control animals which received sodium iodbenzoate or no injection at all. This suggests a relationship between antibody production and oxidative processes.

Recently, Amberg and Knox[3] have studied the action of iodoxybenzoate of sodium on the local allergic reaction. They found that it diminishes the intensity of the intracutaneous reaction when given intravenously in rabbits. Iodbenzoic acid does not have this effect. Given intravenously in a sensitized dog it does not interfere with the fall of blood pressure on re-injection of serum. Hence it does not influence the mechanism of the allergic reaction as such, but acts on the inflammatory processes due to a product of the allergic reaction. These inflammatory processes are, on the other hand, favored by sodium cyanide. Because of these interesting properties of sodium iodosobenzoate and sodium iodoxybenzoate, especially the fact that they contain physiologically available oxygen, appear to stimulate the production of antibodies, and at the same time have marked germicidal properties, I have studied their action on phagocytosis *in vitro*.

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[1] *Ibid.*, p. 145.

[2] *Proc. Chicago Path. Soc.*, 1911, 8, p. 138.

[3] *Jour. Pharm. and Exper. Ther.*, 1912, 3, p. 223.

Equal parts of human serum, the substance studied, washed human leukocytes, and suspension of the organism used were drawn up into capillary pipettes, mixed, and incubated at 37° C. for 20 minutes. Smears were then made, allowed to dry in the air, and stained with methyl thionin. Counts were made of the number of bacteria in at least 100 leukocytes from each smear. The same suspension of organisms as well as leukocytes and serum were used throughout each series, the dilution of the substance studied being varied. These dilutions were made in sterile physiological salt solution.

1. SODIUM IODOXYBENZOATE AND STAPHYLOCOCCUS AUREUS.

Mixtures				Phagocytic Index
Serum	+ salt solution	+ leukocytes	+ staphylococcus	1.8
"	+ N/20 iodoxybenzoate	+ "	+ "	2.5
"	+ N/50 "	+ "	+ "	5.6
"	+ N/100 "	+ "	+ "	3.7
"	+ N/500 "	+ "	+ "	2.8
"	+ N/2,000 "	+ "	+ "	3.0

2. SODIUM IODOXYBENZOATE AND STREPTOCOCCUS PYOGENES.

Mixtures				Phagocytic Index
Salt sol.	+ salt solution	+ leukocytes	+ streptococcus	0.81
"	+ N/50 iodoxybenzoate	+ "	+ "	0.82
Serum	+ salt solution	+ "	+ "	3.5
"	+ N/20 iodoxybenzoate	+ "	+ "	3.5
"	+ N/50 "	+ "	+ "	6.4
"	+ N/500 "	+ "	+ "	5.5
"	+ N/2,000 "	+ "	+ "	5.9

3. SODIUM IODOXYBENZOATE AND PNEUMOCOCCUS.

Mixtures				Phagocytic Index
Serum	+ salt solution	+ leukocytes	+ pneumococcus	2.0
"	+ N/50 iodoxybenzoate	+ "	+ "	2.3
"	+ N/500 "	+ "	+ "	2.4
"	+ N/2,000 "	+ "	+ "	2.1

From these results it is seen that sodium iodoxybenzoate has a marked stimulating action on the phagocytosis of staphylococcus and of streptococcus *in vitro*. This action is not shown by sodium iodbenzoate, which contains no oxygen. The stimulating action is exerted only in the presence of serum, hence the opsonin of the serum is probably rendered more active by the oxygen-containing substances.

The study of the phagocytic index with pneumococcus shows practically no action at all. Dr. E. C. Rosenow tested these substances for their germicidal action toward pneumococcus and found that they have no germicidal action on this organism and instead preserve the cocci from disintegration for a longer time. Did these substances act on the leukocytes, the phagocytosis of pneumococcus should also be stimulated.

These results seem to indicate that the germicidal action of the substances is in some way related to their stimulating effect on phagocytosis, and that both of these properties are the result of the presence in the molecule of physiologically active oxygen attached to the iodin atom. These substances are the only ones thus far known which have a marked germicidal action and at the same time stimulate phagocytosis. That the oxygen is the important factor in the effect on phagocytosis is also indicated by the fact that the cyanides which have an antagonistic action by hindering oxidation also cause marked depression of phagocytosis.

4. POTASSIUM CYANIDE AND STREPTOCOCCUS.

		Mixtures		Phagocytic Index
Serum	+ salt solution	+ leukocytes	+ streptococcus	1.74
Salt sol.	+ "	+ "	+ "	0.04
Serum	+ KCN m/8	+ "	+ "	0.04
"	+ " m/16	+ "	+ "	0.36
"	+ " m/32	+ "	+ "	0.32
"	+ " m/64	+ "	+ "	0.94
"	+ " m/128	+ "	+ "	1.38
"	+ " m/256	+ "	+ "	1.68
"	+ salt solution	+ "	+ "	1.78

Since the sodium iodoso- and iodoxybenzoates are able to stimulate the production of antibodies and cause a leukocytosis and can stimulate phagocytosis *in vitro*, they may be of some value in infections.

CONCLUSIONS.

1. Sodium iodoxybenzoate, which contains 11.43 per cent of physiologically active oxygen, has a markedly stimulating action on the phagocytosis of streptococcus and staphylococcus by human leukocytes in the presence of human serum, *in vitro*.

2. Sodium iodbenzoate, which contains no oxygen, has no such effect.

3. This stimulating effect on phagocytosis is related to its germicidal action, which is also dependent on the oxygen combined with the iodin in the molecule.

4. The opsonin of the serum is probably rendered more active by the oxygen-containing substance, for the stimulating effect is exerted only in the presence of serum.

5. Potassium cyanide, whose action is to depress oxidation, has a markedly depressing effect on phagocytosis.

6. Sodium iodoxybenzoate may be of value in some infections because of its stimulating effect on the production of antibodies and on phagocytosis, as well as its bactericidal action.

7. Furthermore, a relationship is suggested between oxidation and the process of phagocytosis, for a substance which liberates oxygen readily stimulates phagocytosis, whereas a substance which prevents oxidation reduces phagocytosis. It would be interesting to study the effect of oxidation on the immune processes.